WHAT IS CLAIMED IS:

1. A method for modifying a preselected DNA sequence in a cell of a non-inbred animal by homologous recombination between a native target DNA sequence in the preselected DNA sequence and a targeting DNA sequence introduced into the cell, said method comprising:

isolating cells in which preselected sequence modifications have been incorporated into the genome by homologous recombination between the target DNA and the targeting DNA, wherein the target DNA and the targeting DNA are substantially isogenic except for the preselected sequence modifications.

2. A method according to claim 1, wherein the animal cell is a mammalian cell.

3. A method according to claim 1, wherein the sequence modifications in the targeting DNA comprise an insertion of a selectable marker.

4. A method according to claim 3, wherein the selectable marker is a gene conferring resistance to an inhibitory compound.

5. A method according to claim 4, wherein the gene conferring resistance to an inhibitory compound substantially lacks its own transcriptional and/or translational start signals.

6. A method according to claim 4, wherein the gene conferring resistance to an inhibitory compound is preferentially expressed when integrated into the genome by homologous recombination between the targeting DNA sequence and the target DNA sequence.

7. A method according to claim 3, wherein the selectable marker is a gene conferring the ability to grow on a selected substrate.

8. A method according to claim 1, wherein the targeting DNA sequence is at least about 99% identical with the target DNA sequence except for the desired sequence modifications.

9. A method for modifying a non-murine animal cell genome by homologous recombination between a target DNA sequence in the animal cell genome and a targeting DNA sequence introduced into the animal cell, said method comprising:

introducing into cells to be targeted a DNA delivery molecule comprising the targeting DNA; and

isolating cells in which preselected sequence modifications have been incorporated into the genome by homologous recombination between the target DNA and the targeting DNA, wherein the target DNA and the targeting DNA are substantially isogenic except for the preselected sequence modifications.

10. A method according to claim 9, wherein the targeting DNA is introduced into the cell by microinjection.

11. A method according to claim 9, wherein the targeting DNA sequence is at least about 99.5-99.9% identical with the target DNA sequence except for the desired sequence modifications.

12. A method according to claim 9, wherein the native target DNA is an immunoglobulin gene.

13. A method according to claim 9, wherein the targeting DNA comprises an isogenic sequence of about 75 to 150 base pairs that is identical with a corresponding sequence in the target DNA.

14. A method according to claim 9, wherein the sequence modifications in the targeting DNA comprise one or more modifications selected from the group consisting of insertions, deletions and substitutions.

15. A method for modifying a cell genome of an animal by homologous recombination between a target DNA sequence in the animal cell genome and a targeting DNA sequence introduced into the animal cell, said method comprising:

introducing a DNA delivery molecule comprising the targeting DNA into cells to be targeted, wherein the targeting DNA was prepared from cells of the same individual animal or a sibling thereof; and

isolating cells in which preselected sequence modifications have been incorporated into the genome by homologous recombination between the target DNA and the targeting DNA, wherein the target DNA and the targeting DNA are substantially isogenic except for the preselected sequence modifications.

16. A method for enhancing homologous recombination between a native target DNA sequence in a non-murine mammalian cell line and a targeting DNA sequence introduced into the cell line, said method comprising the steps of:

isolating targeting DNA derived from a second cell line wherein said targeting DNA is substantially isogenic with the target DNA; and

introducing desired sequence modifications into the targeting DNA; and

introducing a DNA delivery molecule comprising the targeting DNA into cells to be targeted; and

isolating cells in which one or more of the sequence modifications are incorporated into the genome by homologous recombination between the target DNA and the targeting DNA.

17. A method according to claim 16, wherein the second cell line is identical with the mammalian cell line.

18. A method for producing a genetically modified mammal comprising:

modifying the genome of embryonic stem cells of the desired mammal in accordance with claim 1, 9 or 15; and

incorporating the modified embryonic stem cells into a blastocyst derived from said mammal; and

growing the blastocyst into a chimeric animal.

19. A method for producing a genetically modified mammal comprising:

modifying the genome of embryonic stem cells of the desired mammal in accordance with claim 1, 9 or 15; and

incorporating the modified embryonic stem cells into a blastocyst derived from said mammal; and

growing the blastocyst into a chimeric animal.

breeding the chimeric animal to obtain a non-chimeric offspring in which the genetic alteration has been acquired through germ-line transmission.

20. A method for producing a genetically modified animal comprising:

modifying the genome of a zygote of the desired animal in accordance with claim 1, 9 or 15; and

growing the zygote into an animal.

21. A method for gene therapy of an animal comprising:

introducing into cells of a first animal to be targeted a DNA delivery molecule comprising a targeting DNA sequence from a second animal, which sequence is capable of effecting homologous recombination with a substantially isogenic target DNA sequence, other than preselected sequence modifications, in the first animal cell genome;

isolating cells in which the preselected sequence modifications have been incorporated into the genome; and

introducing the modified cells into the first animal.

22. A method according to claim 21, wherein the first animal and the second animal are members of the same species.

23. A method according to claim 21, wherein the first animal is a sibling of the second animal.

24. A method according to claim 21, wherein the cells are somatic cells.

25. A method according to claim 21, wherein the cells are hematopoietic cells.

26. A method according to claim 21, wherein modifying the genome comprises correcting a defective gene.

27. A method according to claim 21, wherein modifying the genome comprises inactivating a gene.

28. A composition comprising a collection of cells between about 10 to 90% of which exhibit a recombination event at a preselected native target DNA segment of the cells, which recombination event is selected from the group consisting of an addition of an exogenous DNA segment to the native DNA segment, a substitution of an exogenous DNA segment for the native DNA segment, and a deletion of the native DNA segment from the cell; wherein genomes of the cells exhibiting the event consist essentially of substantially isogenic DNA proximate to the recombination event except for the exogenous DNA.

29. A composition of claim 28, wherein about 30% of the cells exhibit the recombination event.

30. A component of claim 28, wherein the cells are isolated from an in-bred mouse.

31. A composition of claim 28, wherein the exogenous DNA segment is from a cell of a different species than cells in the collection.

32. A non-human animal comprising cells with a homologous recombination event at a preselected native target DNA segment in the cell genome, wherein genomes of the cells consist essentially of substantially isogenic DNA proximate to the target DNA segment except for preselected sequence modifications which are incapable of undergoing homologous recombination in the cells unless linked to a second DNA segment homologous to the native target DNA segment.

33. A non-human animal of claim 32, wherein the recombination event is a deletion, insertion or substitution.

34. A non-human animal of claim 32, wherein the cells are murine.

35. A non-human animal of claim 34, wherein the mouse cells comprise a DNA segment from a different manual.

36. A non-human animal of claim 35, wherein the DNA segment encodes a human immunoglobulin gene.